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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,880	06/22/2001	Jason Francis Conaty	65340/JPW/GJG	4388

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EXAMINER
EPPS FORD, JANET L

ART UNIT	PAPER NUMBER
1635	12

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/887,880	CONATY ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-20,23 and 32-36* is/are allowed.

6)☒ Claim(s) *21-22, 24* *25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Claims 1-20, 23 and 32-36 are directed to an allowable product. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims 25-31, directed to the process of making or using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Claims 25-31 are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Since all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, the restriction requirement made in Paper No. 8 is hereby withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21-22, and 24-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of the present invention to cleave RNA *in vitro*, does not reasonably provide enablement for using the claimed compounds *in vivo,* to cleave RNA for treatment purposes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 21-22, and 24 are drawn to host cells transformed by a vector comprising the compounds according to the present invention, wherein said host cell reads on transformation of a whole animal, including a human administered said vector, and further wherein said host cells

read on a transgenic animal, including a human. Claims 25-31 recite a method of cleaving a target mRNA in a subject which comprises administering the compounds according to the present invention to a subject. The instant claims encompass wherein the compounds of the present invention are administered for therapeutic purpose.

In the instant case it is concluded that the amount of experimentation required to practice the full scope of the claimed invention would be undue based upon the following considerations. The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

The quantity of experimentation required for practicing the invention of claims 25-31 would require determining the structures of the mRNA targets of the compounds of the present invention *in vivo*, wherein cleavage of said mRNA target *in vivo* would produce the desired therapeutic treatment effects in an individual. Additionally, modes of delivery of the compounds according to the present invention, *in vivo,* would have to be determined such that the processing of said mRNA target is inhibited at a significant level and for a sufficient amount of time to produce the desired therapeutic effect. Neither the specification as filed, nor the prior art searched, provides any specific guidelines in this regard. Furthermore, the specification as filed provides guidance for transforming a host cell *in vitro* with the compounds of the present invention. There is no guidance in the specification as filed or by prior art citation that would direct the skilled artisan to make a transgenic animal expressing the vectors according to the

present invention. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In regards to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance or instruction that would teach one of skill in the art how to successfully treat a human having a disease or condition associated the expression of an mRNA target comprising the administration of the compounds or compositions of the present invention for therapeutic purposes. The specification as filed provides only information regarding the ability of compounds according to the present invention to cleave target mRNA *in vitro,* see page 36-38. However, the examples do not provide any direct evidence of phenotypic effects on the treated cells, for example there is no indication that cell growth was inhibited. Furthermore, the instant specification does not provided any clear nexus between cleaving an mRNA target using the compounds of the present invention, and the treatment or prophylaxis of a disease or condition associated with said mRNA target in said human cells or tissues.

Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (1998), states "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]." Furthermore, Crooke describes a variety of factors that influence the behavior of oligonucleotide-based compounds in a cellular environment. Crooke teaches that variations in cellular uptake and distribution of

oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. The influence of non-antisense effects, for example phosphorothioate oligonucleotides tend to bind non-specifically to many proteins, wherein such protein binding influences cellular uptake, distribution, metabolism and excretion of said oligonucleotide. Additionally, non-specific protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors, which influence the behavior of oligonucleotide based, compounds thereby rendering the activity of antisense compounds unpredictable.

Branch (1998) also teach that "Scientist seek to use the molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNA molecules and their association with cellular proteins can render target sites totally unaccessible *in vivo*. Moreover, Branch states that "[H]owever, their *(in referring to antisense molecules and ribozymes)* unpredictability confounds research applications of nucleic acid reagents."

Jen et al. (*Stem Cells,* Vol. 18: 307-319, 2000) provide a review of the challenges that remain before oligonucleotide-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the oligonucleotide based therapy art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that "[G]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also concluded that "[A] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (see page 315, last two paragraphs).

It is apparent from Branch, Crooke, and Jen et al. that the art of oligonucleotide base therapeutics (at the time of filing) is unpredictable and those highly skilled in the art are working towards making the antisense therapy more predictable have many obstacles to overcome. Therefore, claims directed to the use of oligonucleotide based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the art.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the behavior of oligonucleotide based compounds *in vivo,* the delivery of oligonucleotide compounds *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (treating a patient with a disease or

condition associated with the expression of an mRNA target) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Conclusion

4. 1-20, 23 and 32-36 are allowable over the prior art searched, or any combination thereof.

5. According to MPEP § 821.04, "If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action."

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
August 23, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635